PATENT ABSTRACTS OF JAPAN

(11)Publication number : 10-298194
(43)Date of publication of application : 10.11.1998

(51)Int.Cl. C07H 19/073
A61K 31/70
C07H 19/173

(21)Application number : 09-123304
(22)Date of filing : 24.04.1997

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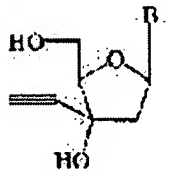
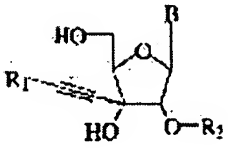
(54) 2-DEOXY-3-ETHYNYL-BETA-D-RIBOFURANOSYL DERIVATIVE

(57)Abstract:
PROBLEM TO BE SOLVED: To provide the subject new nucleic acid derivative consisting of a specific 2-deoxy-3-ethynyl-β-D-ribofuranosyl derivative, exhibiting extremely strong cytocidal activity and excellent antitumor activity and useful as an antitumor agent, etc.
SOLUTION: This derivative is a new 2-deoxy-3-ethynyl-β-D-ribofuranosyl derivative expressed by the formula I (B is a nucleic acid base which may have substituent) and its ester easily decomposable in vivo or its pharmacologically permissible salt. The derivative has excellent antitumor activity and is useful as an antitumor agent, etc. The compound can be produced by reacting a compound of the formula II (R1 and R2 are each a trialkylsilyl) with an acylating agent in a solvent in the presence of a basic catalyst, desilylating the obtained acylated product, reacting the resultant compound of the formula III (Acyl is an acyl) with a tributyltin halide in the presence of azoisobutyronitrile to eliminate the 2-OH group and deacylating the product.



I



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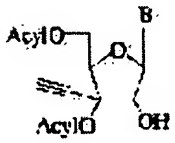


III

LEGAL STATUS

[Date of request for examination] 08.11.2001
[Date of sending the examiner's decision of rejection]
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]
[Date of final disposal for application]
[Patent number]
[Date of registration]
[Number of appeal against examiner's decision of rejection]
[Date of requesting appeal against examiner's decision of rejection]
[Date of extinction of right]

EFFECT OF THE INVENTION

[Effect of the Invention] The new 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative of this invention has the antitumor activity which was excellent, for example, and is useful as an antitumor agent.

[Translation done.]

PRIOR ART

[Description of the Prior Art] Conventionally, as an antitumor agent which is an antimetabolite of a nucleic-acid system, pyrimidine system compounds, such as 5-fluorouracil, tegafur, UFT (UFT), doxifluridine, carmofur, cytarabine, and enocitabine, are known. As the nucleoside which has an alkynyl group in the 3rd place of a PENTO furanose, Chem.Pharm.Bull 35 (6) 2605-2608 To (1987), 1-[2, 5-G In a (tert-butyldimethylsilyl)-3-C-FENECHINIRU-beta-D-RIBO-PENTO furanosyl] uracil list, 1-[2 and 5-G (tert-butyldimethylsilyl)-3-C-FENECHINIRU-beta-D-RIBO-PENTO furanosyl] adenine Tetrahedron Letters and 36(7)1031- a 1-[2-O-(tert-butyldimethylsilyl)-3-C-ethynyl-beta-D-RIBO-PENTO furanosyl thymine to 1034 and 1995 Although the 1-[2-O-(tert-butyldimethylsilyl)-3-C-ethynyl-beta-D-RIBO-PENTO furanosyl thymine is indicated by Tetrahedron and 47(9)1727-1736 (1991), respectively, the pharmacological action is not indicated. Moreover, although indicated by the patent international public presentation 96/No. 18636 for which this invention persons applied previously as a 3-ethynyl-beta-D-ribofuranosyl derivative, the 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative is not yet known.

[Translation done.]

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

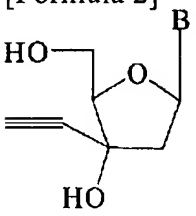
TECHNICAL FIELD

[Field of the Invention] This invention relates to a new nucleic-acid derivative. The compound of this invention has the antitumor activity which was excellent, for example, and is useful as an antitumor agent.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to a new nucleic-acid derivative. The compound of this invention has the antitumor activity which was excellent, for example, and is useful as an antitumor agent.
[0002]
[Description of the Prior Art] Conventionally, as an antitumor agent which is an antimetabolite of a nucleic-acid system, pyrimidine system compounds, such as 5-fluorouracil, tegafur, UFT (UFT), doxifluridine, carmofur, cytarabine, and enocitabine, are known. As the nucleoside which has an alkynyl group in the 3rd place of a PENTO furanose, Chem.Pharm.Bull 35 (6) 2605-2608 To (1987), 1-[2, 5-G In a (tert-butyldimethylsilyl)-3-C-FENECHINIRU-beta-D-RIBO-PENTO furanosyl] uracil list, 1-[2 and 5-G (tert-butyldimethylsilyl)-3-C-FENECHINIRU-beta-D-RIBO-PENTO furanosyl] adenine Tetrahedron Letters and 36(7)1031- a 1-[2-O-(tert-butyldimethylsilyl)-3-C-ethynyl-beta-D-RIBO-PENTO furanosyl thymine to 1034 and 1995 Although the 1-[2-O-(tert-butyldimethylsilyl)-3-C-ethynyl-beta-D-RIBO-PENTO furanosyl thymine is indicated by Tetrahedron and 47(9)1727-1736 (1991), respectively, the pharmacological action is not indicated. Moreover, although indicated by the patent international public presentation 96/No. 18636 for which this invention persons applied previously as a 3-ethynyl-beta-D-ribofuranosyl derivative, the 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative is not yet known.
[0003]
[Problem(s) to be Solved by the Invention] The purpose of this invention is to have the outstanding antitumor activity and offer a new 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative useful as an antitumor agent.
[0004]
[Means for Solving the Problem] This invention relates to the 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative expressed with a general formula (1) and its ester from which it may be desorbed easily in the living body, or the salt permitted pharmacologically.
[0005]
[Formula 2]



(1)

(B shows among a formula the nucleobase which may have a substituent.)
[0006] this invention person showed the antitumor activity in which the nucleic-acid derivative which introduced the ethynyl group into the 3rd place of a 2-deoxy PENTO furanose was excellent as a result of repeating research wholeheartedly, and a header and this invention were completed for it being useful as an antitumor agent.
[0007] As a nucleobase expressed with B, purine bases, such as pyrimidine bases, such as a cytosine, a uracil, and a thymine, an adenine, and a guanine, are mentioned among the above-mentioned general formula (1), for example. As the substituent, permutation oxy-carbonyl groups, such as a halogen atom, low-grade alkyl group, and aliphatic series acyl group or acyl groups, such as an aromatic series acyl group, a low-grade alkoxy carbonyl group, a low-grade alkenyloxy carbonyl group, or an aralkyloxy carbonyl group, etc. are mentioned, for example. As a halogen atom, for example, a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, etc. are mentioned. As a low-grade alkyl group, the alkyl group of the shape of the shape of a straight chain of the carbon numbers 1-6, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and a hexyl group, and branching is mentioned, for example. For example, as an aliphatic series acyl group, the acyl group of the shape of the shape of a straight chain of

the carbon numbers 1-6, such as the formyl, acetyl, a propionyl, butyryl, isobutyryl, PENTA noil, and a hexa noil radical, and branching is mentioned, and benzoyl, alpha-naphthoyl, beta-naphthoyl radical, etc. are mentioned as an aromatic series acyl group. Moreover, these may have the low-grade alkyl group, the lower alkoxy group, the halogen atom, the nitro group, etc. as a substituent. The thing same as a low-grade alkyl group and halogen atom as the above is mentioned. As a lower alkoxy group, the alkoxy group of the shape of the shape of a straight chain of the carbon numbers 1-6, such as methoxy and ethoxy **n-propoxy, isopropoxy, n-butoxy, iso butoxy, sec-butoxy, tert-butoxy, pentyloxy one, and a hexyloxy radical, and branching is mentioned, for example.

[0008] As a low-grade alkoxy carbonyl group, the alkoxy carbonyl group of the shape of the shape of a straight chain of the carbon numbers 2-7, such as methoxycarbonyl, ethoxycarbonyl, n-propoxy carbonyl, isopropoxycarbonyl, n-butoxycarbonyl, iso butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxy carbonyl, and a hexyloxy carbonyl group, and branching is mentioned, for example. As a low-grade alkenyloxy carbonyl group, the alkenyloxy carbonyl group of the shape of the shape of a straight chain of the carbon numbers 3-7, such as vinyloxycarbonyl, allyloxy carbonyl, isopropenyl oxy-carbonyl, 1-butenyl oxy-carbonyl, and 2-butenyl oxy-carbonyl group, and branching is mentioned, for example. As an aralkyloxy carbonyl group etc., the aralkyloxy carbonyl group of the carbon numbers 8-12, such as benzyloxycarbonyl, phenethyloxy carbonyl, alpha-naphthlmethyloxy carbonyl, and beta-naphthlmethyloxy carbonyl group, is mentioned, for example, and these may have the low-grade alkyl group, the lower alkoxy group, the halogen atom, the nitro group, etc. as a substituent.

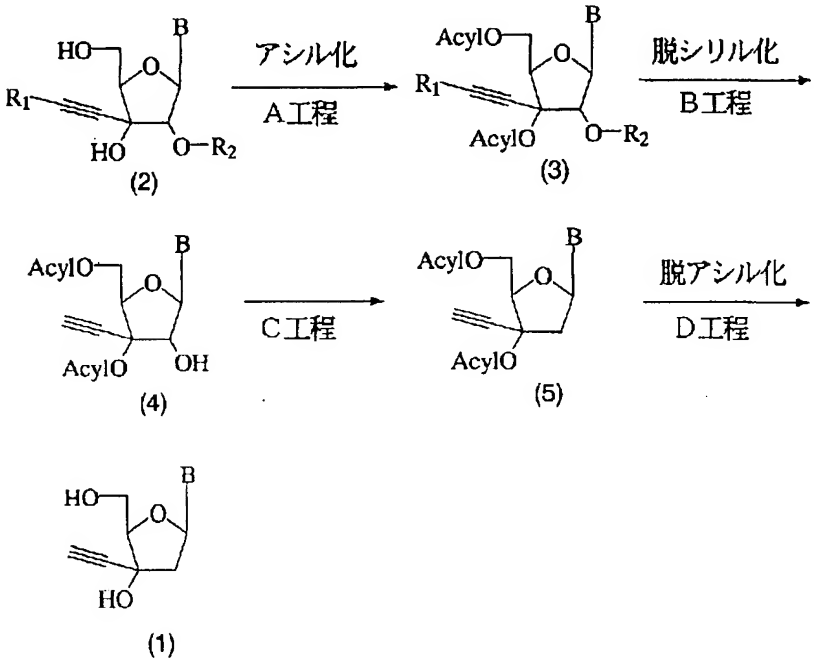
[0009] With the ester formation residue from which it may be desorbed easily in the living body The nonpoisonous ester group which emits the compound which cleaves easily by the blood and the in-house of mammalian which form 3 and the hydroxyl group of the 5th place, and ester of a compound which are expressed with a general formula (1), and contain Homo sapiens, and is expressed with a general formula (1) is meant. That what is necessary is just what protects the hydroxyl group of a nucleoside usually well known as this ester group, and forms ester For example, acyl groups, such as an aromatic series acyl group which may have the aliphatic series acyl group or substituent which may have a substituent, an aryloxy carbonyl group, a low-grade alkoxy carbonyl group, a low-grade alkyl carbamoyl group, amino acid residue, etc. are mentioned. As an acyl group of the aliphatic series which may have the substituent, or aromatic series, a low-grade alkanoyl radical, an aryl carbonyl group, a heterocycle carbonyl group, an acyloxy acyl group, etc. are mentioned, for example. The alkanoyl radical of the carbon numbers 1-6 which have had the halogen atom, the lower alkoxy group, etc. as a low-grade alkanoyl radical, for example as substituents, such as the formyl, acetyl, a propionyl, the butyryl, isobutyryl, PENTA noil, hexa noil, chloro acetyl, dichloro acetyl, trichloroacetyl, trifluoro acetyl, methoxy acetyl, and an ethoxy acetyl group, is mentioned.

[0010] As an aryl carbonyl group, for example Benzoyl, alpha-naphthyl carbonyl, beta-naphthyl carbonyl, 2-methyl benzoyl, 3-methyl benzoyl, 4-methyl benzoyl, 2, 4-dimethylbenzoyl, 4-ethyl benzoyl, 2-methoxy benzoyl, 3-methoxy benzoyl, 4-methoxy benzoyl, 2, 4-dimethoxybenzoyl, 4-ethoxy benzoyl, 2-methoxy-4-ethoxy benzoyl, 4-propoxy benzoyl, 2-chloro benzoyl, 3-chloro benzoyl, 4-chloro benzoyl, 2, 3-dichlorobenzoyl, 2-BUROMO benzoyl, 4-fluoro benzoyl, 2-carboxy benzoyl, 3-carboxy benzoyl, 4-carboxy benzoyl, 2-cyano benzoyl, 4-cyano benzoyl, The benzoyl which has had a low-grade alkyl group, a lower alkoxy group, the halogen atom, the carboxyl group, the cyano group, the nitro group, etc. as substituents, such as 2-nitrobenzoyl, 4-nitrobenzoyl, 2, and 4-dinitro benzoyl, a naphthyl carbonyl group, etc. are mentioned.

[0011] As a heterocycle carbonyl group, 2-furanyl carbonyl, 4-thiazolyl carbonyl, 2-quinolyl carbonyl, 2-pyrazinyl carbonyl, 2-pyridyl carbonyl, 3-pyridyl carbonyl, 4-pyridyl carbonyl group, etc. are mentioned, for example. As an acyloxy acyl group, acetyloxy acetyl, propionyloxy acetyl, alpha-(acetyloxy) propionyl, beta-(propionyloxy) propionyl radical, etc. are mentioned, for example. As an aryloxy carbonyl group, for example Phenoxy carbonyl, alpha-naphthyloxy carbonyl, beta-naphthyloxy carbonyl, 2-methylphenoxy carbonyl, 3-methylphenoxy carbonyl, 4-methylphenoxy carbonyl, 2, 4-dimethyl phenoxy carbonyl, 4-ethyl phenoxy carbonyl, 2-methoxy phenoxy carbonyl, 3-methoxy phenoxy carbonyl, 4-methoxy phenoxy carbonyl, 2, 4-dimethoxy phenoxy carbonyl, 4-ethoxy phenoxy carbonyl, 2-methoxy-4-ethoxy phenoxy carbonyl, 2-chloro phenoxy carbonyl, 3-chloro phenoxy carbonyl, 4-chloro phenoxy carbonyl, 2, 3-dichloro phenoxy carbonyl, 2-BUROMO phenoxy carbonyl, 4-fluorophenoxy carbonyl, beta-methyl-alpha-naphthyloxy carbonyl, a beta-chloro-alpha-naphthyloxy carbonyl group, etc. are mentioned.

[0012] As a low-grade alkoxy carbonyl group, the alkoxy carbonyl group of the shape of the shape of a straight chain of the carbon numbers 2-7, such as methoxycarbonyl, ethoxycarbonyl, n-propoxy carbonyl, isopropoxycarbonyl, n-butoxycarbonyl, iso butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxy carbonyl, and a hexyloxy carbonyl group, and branching is mentioned, for example. As a low-grade alkyl carbamoyl group, monochrome or the carbamoyl group by which the JI permutation was carried out is mentioned, for example by the alkyl group of the shape of the shape of a straight chain of the carbon numbers 1-6, such as methyl carbamoyl, ethyl carbamoyl, propyl carbamoyl, butylcarbamoyl, pentyl carbamoyl, hexyl carbamoyl, dimethyl carbamoyl, and a diethylcarbamoyl radical, and branching. Although the radical formed except for a hydroxyl group as amino acid residue from the carboxyl group of amino acid is shown and a glycine, an alanine, the beta-alanine, a valine, an isoleucine, etc. are mentioned as a

heavens NO acid, for example, you may be any as long as it is amino acid residue given in JP,1-104093,A.
[0013] in addition, as an ester group For example, THEODORA W.GREENE, "PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition", JOHN WILEY & SONS, INC. (1991), the edited by Chemical Society of Japan -- <new experimental science lecture 4> "composition [of an organic compound] and reaction (V)" 11 chapter p2495 Maruzen (1983) -- You may be any although commonly used by JP,61-106593,A, JP,62-149696,A, and JP,1-153696,A as a usual ester group of a publication. As B, cytosine, uracil, thymine, adenine, guanine, 5-fluoro cytosine, 5-fluorouracil, 5-BUROMO cytosine, 5-bromouracil, 4-N-methylcytosine or 4-N, and N-dimethyl cytosine is mentioned suitably, and a cytosine, a uracil, a thymine, and an adenine are mentioned still more suitably. As ester formation residue from which it may be desorbed easily in the living body, an acyl group is mentioned suitably and an acetyl group and benzoyl are mentioned still more suitably.
[0014] this invention compound also includes the gestalt of a salt, if it is the salt pharmacologically permitted as this salt, there will be especially no limit and acid addition salts, such as organic-acid salts, such as aliphatic series carboxylate, such as organic sulfonates, such as inorganic-acid salts, such as a hydrochloride, hydrobromate, and a sulfate, a methansulfonic acid salt, and a benzenesulfonic acid salt, acetate, propionate, and a trifluoroacetic acid salt, will be illustrated. Moreover, this invention compound also includes the hydrate. this invention compound expressed with a general formula (1) can be manufactured for example, according to the following reaction process type.
[0015]
[Formula 3]
<反応工程式>



(the inside of a formula, and B -- the above -- the same -- R1 and R2 show a trialkylsilyl group, and Acyl shows a protection acyl group)
[0016] (A process) The compound expressed with a general formula (3) is obtained by making the compound expressed with a general formula (2) react with an acylating agent under existence of a basic catalyst or nonexistence in a solvent. the compound expressed with a general formula (2) -- Tetrahedron Letters and 36(7)1031- although it is the well-known compound compounded by the approach indicated by 1034 and 1995 or is compounded according to a well-known approach, it is manufactured by the approach specifically indicated for the example of the after-mentioned reference. The trialkylsilyl group permuted as a trialkylsilyl group expressed with R1 and R2 by the low-grade alkyl group of the carbon numbers 1-6, such as trimethylsilyl, triethyl silyl, tert-butyldimethylsilyl, and triisopropyl silyl, is used. As an acylating agent, the thing of well-known common use, such as aromatic carboxylic acid, such as low-grade aliphatic carboxylic acid of the carbon numbers 2-6, such as an acetic acid, a propionic acid, and butanoic acid, a benzoic acid, and p-nitrobenzoic acid, those acid halides, and an acid anhydride, can be used. Although it is not limited especially unless a reaction is affected as a solvent, an acetonitrile, a tetrahydrofuran, nitromethane, a methylene chloride, etc. can be illustrated. p-dimethylamino pyridine (DMAP) etc. is mentioned as a basic catalyst. A reaction rate is good 3 - 10 time molar quantity and to carry out molar quantity use of the acylating agent 1- 5 times preferably to the compound of a general formula (2). 0-150 degrees C of reaction temperature are room temperature -100 degree C preferably, and reaction time completes a reaction in 0.1 - 100 hours.

[0017] (B process) The compound which performs desilanizing and is expressed with a general formula (4) is obtained by making the compound expressed with a general formula (3) react with an acid in a solvent. An acetonitrile, a tetrahydrofuran, etc. are mentioned, although it is not limited especially unless a reaction is affected as a solvent. As an acid, a hydrochloric acid, a sulfuric acid, an acetic acid, etc. can be used. The rate of a reaction is good to carry out molar quantity use of the acid 2- 10 times to the compound of a general formula (3). 0-80 degrees C of reaction temperature are room temperature extent preferably, and reaction time is 5 - 24 hours.
[0018] (C process) without it makes the compound expressed with a general formula (4) react with 1 and 1'-thio carbonyldiimidazole in a solvent, and it isolates the purpose intermediate product continuously or it isolates -- trialkyl- as it is CHINHA idola, such as existence[azo-isobutyro-dinitrile (azobisuisobutironitoriru)]-izing and tributyltin hydride, -- the compound which the hydroxyl group of the 2nd place is desorbed and is expressed with a general formula (5) is obtained by making it react with the id. Although it is not limited especially unless a reaction is affected as a solvent, an acetonitrile, a tetrahydrofuran, a methylene chloride, benzene, etc. are mentioned. a reaction rate -- the compound of a general formula (4) -- receiving -- 1 and 1'-thio carbonyldiimidazole -- 1.5 - 10 time molar quantity -- desirable -- 2 - 4 time molar quantity and azobisuisobutironitoriru -- 0.1 - 0.5 time molar quantity and trialkyl CHINHA idola -- it is good to carry out molar quantity use of the id 4- 10 times. Reaction temperature is the boiling point temperature of 0 degree C - a solvent, and, in reaction time, a reaction advances advantageously in 3 - 12 hours.
[0019] (D process) The compound which performs a deacylation and is expressed with a general formula (1) is obtained by making the compound expressed with a general formula (5) react with a base in a solvent. A methanol, ethanol, etc. can be illustrated, although it is not limited especially unless a reaction is affected as a solvent. As a base, a sodium hydroxide, a potassium hydroxide, sodium methylate, etc. are mentioned. A reaction rate is good 0.1 - 10 time molar quantity and to carry out molar quantity use of the base 0.5- 1 time preferably to the compound of a general formula (5). 0-100 degrees C of reaction temperature are room temperature -70 degree C preferably, and reaction time completes a reaction in 2 - 5 hours. Isolation purification is possible for this invention compound obtained by the above-mentioned approach by usually using a well-known separation purification means, for example, concentration, solvent extraction, filtration, recrystallization, various chromatographies, etc.
[0020] The compound of this invention can make this a physic constituent according to the usual approach using the medicinal and suitable pharmacological support made into an active principle. As support used here, various kinds of things used widely by the usual drugs, for example, an excipient, a binder, disintegrator, lubricant, a coloring agent, corrigent, an odor-masking agent, a surfactant, etc. can be used. Especially the administration unit form voice at the time of using this invention physic or a physic constituent as a therapy agent of the neoplasm of mammalian including Homo sapiens is not limited, but can be suitably chosen according to the therapy purpose, and the oral agent of parenteral agents, such as injections, suppositories, external preparations (an ointment, patches, etc.), and aerosols, a tablet, a covering tablet, powder, a granule, a capsule, a pill, and liquids and solutions (suspension, emulsion, etc.) is specifically mentioned.
[0021] The various above-mentioned constituents are pharmaceutical-preparation-ized by the pharmaceutical preparation-ized approach usually learned for this field. It faces fabricating in the gestalt of injections and stabilizing agents, such as pH regulators, such as diluents, such as water, ethyl alcohol, macro gall, propylene glycol, ethoxylation isostearyl alcohol, polyoxy-ized isostearyl alcohol, and polyoxyethylene sorbitan fatty acid ester, a sodium citrate, sodium acetate, and sodium phosphate, and a buffer, a sodium pyrosulfite, ethylenediaminetetraacetic acid, thioglycolic acid, and thiolactic acid, etc. can be used as support. In addition, the salt, the grape sugar, or the glycerol of sufficient amount to prepare an isosmotic solution in this case may be made to contain in physic pharmaceutical preparation, and the usual solubilizing agent, an aponia-ized agent, local anesthetic, etc. may be added. Such support can be added and hypodermically, intramuscular, and vein internal use injections can be manufactured with a conventional method.
[0022] It faces fabricating in the gestalt of suppositories, and the absorption enhancers suitable as support for the ester of a polyethylene glycol, cacao butter, lanolin, higher alcohol, and higher alcohol, gelatin, semisynthetic glyceride, witepsol (trademark: dynamite Nobel), etc. can be added and used. In case it prepares in the gestalt of an ointment, for example, a paste, a cream, and gel, the basis usually used, a stabilizer, a wetting agent, a preservative, etc. are blended if needed, and are mixed and pharmaceutical-preparation-ized by the conventional method. White vaseline, paraffin, a glycerol, a cellulosic, a polyethylene glycol, silicon, a bentonite, etc. can be used as a basis. As a preservative, methyl parahydroxybenzoate, ethyl p-hydroxybenzoate, propyl parahydroxybenzoate, etc. can be used. What is necessary is just to apply the above-mentioned ointment, a cream, a paste, gel, etc. to the usual base material with a conventional method, in manufacturing patches. As a base material, a film or foam sheets, such as textile fabrics which consist of cotton, a staple fiber, and a chemical fiber, a nonwoven fabric, an elasticity vinyl chloride, polyethylene, and polyurethane, etc. are suitable.
[0023] It faces preparing in the gestalt of solid preparations for taking orally, such as a tablet, powder, and a granule. As support, for example, a lactose, white soft sugar, a sodium chloride, grape sugar, a urea, starch, A calcium carbonate, a kaolin, crystalline cellulose, a silicic acid, methyl cellulose, Excipients, such as a glycerol, sodium

alginate, and gum arabic, simple syrup, Grape-sugar liquid, starch liquid, a gelatin solution, polyvinyl alcohol, polyvinyl ether, A polyvinyl pyrrolidone, a carboxymethyl cellulose, a shellac, methyl cellulose, Binders, such as ethyl cellulose, water, ethanol, and potassium phosphate, desiccation starch, Sodium alginate, agar powder, the end of a laminaran, a sodium hydrogencarbonate, A calcium carbonate and polyoxyethylene sorbitan fatty acid ester Sodium lauryl sulfate, a stearin acid monoglyceride, starch, Collapse inhibitors, such as disintegrator, such as a lactose, white soft sugar, stearin acid, cocoa butter, and hydrogenated oil, Absorption enhancers, such as a quarternary-ammonium-salt radical and sodium lauryl sulfate, Lubricant, such as a polyethylene glycol, etc. can be used in adsorbents, such as moisturizers, such as a glycerol and starch, starch, a lactose, a kaolin, a bentonite, and a colloid silicic acid, purification talc, a stearate, and the end of a boric acid. Furthermore, a tablet can be used as the tablet which gave the usual coating if needed, for example, a sugar-coated tablet, a gelatin encapsulation lock, an enteric tablet, a film coated tablet, an auxiliary rim lock, a multilayered tablet, etc.

[0024] A capsule is mixed with various kinds of support illustrated above, and a hard gelatine capsule, an elasticity capsule, etc. are filled up with it, and it is prepared. It faces fabricating in the gestalt of a pill and disintegrator, such as binders, such as excipients, such as grape sugar, a lactose, starch, cacao butter, hardening vegetable oil, a kaolin, and talc, gummi arabicum pulveratum, powdered tragacanth, gelatin, and ethanol, a laminaran, and agar, etc. can be used as support. Liquid pharmaceutical preparation may be water or oily suspension, a solution, syrup, and elixirs, and these are prepared according to a conventional method using the usual additive. Although the amount of this invention compound which should be contained in the above-mentioned pharmaceutical preparation changes with a pharmaceutical form, a route of administration, dosage regimen, etc. and is generally chosen from ******** and the large range suitably, it is usually good in pharmaceutical preparation to consider as about 1 - 70 % of the weight.

[0025] Especially the medication method of the above-mentioned pharmaceutical preparation is not limited, but it opts for enteral administration, internal use, rectum administration, the administration in the oral cavity, dermal administration, etc. suitably, corresponding to the age for [, such as a gestalt of pharmaceutical preparation, and a patient] administration, the conditions of sex and others, extent of a symptom, etc. For example, in the case of a tablet, a pill, liquids and solutions, suspension, an emulsion, a granule, and a capsule, it is administered orally, and, in the case of suppositories, intrarectal administration is carried out. the case of injections -- independent -- or it mixes with the usual water additions, such as grape sugar and amino acid, and administers intravenously -- having -- further -- the need -- responding -- independent -- the inside of the inside of an artery, intramuscular, and a hide, and hypodermically -- or intraperitoneal administration is carried out. An ointment is applied to the skin, the membrane in the oral cavity, etc. Although the dose of the compound of this invention is suitably chosen according to the age for [, such as direction for use and a patient,] administration, sex, a condition, the class of neoplasm, the class of this invention compound prescribed for the patient, other conditions, etc., generally it is desirable in an oral agent per administration unit form voice for it to be referred to as about 0.1-500mg in about 1-1000mg and injections, and to be referred to as about 5-1000mg in suppositories. Moreover, the dose per day of the drugs which have the above-mentioned administration gestalt is [0.1 - 200 mg/kg weight / whenever / schedule] usually preferably good to make the amount used as the range of 0.5 - 100 mg/kg weight / whenever [schedule] into a standard. These this invention pharmaceutical preparation can be prescribed for the patient in 1 time or about 2 - 4 steps on the 1st.

[0026] As a neoplasm which can be treated by prescribing the pharmaceutical preparation containing this invention compound for the patient, there is especially no limit, for example, head neck cancer, an esophagus cancer, gastric cancer, colon cancer, rectal cancer, liver cancer, the gallbladder and a cholangioma, a pancreatic cancer, lung cancer, a breast cancer, an ovarian cancer, vesical cancer, a prostatic cancer, the orchioncus, a bone and soft-parts sarcomata, a malignant lymphoma, leukemia, a cervical carcinoma, skin carcinoma, a brain tumor, etc. are mentioned.

[0027]

[Example] Although the example of reference, an example, and the example of a pharmacological test are shown below and this invention is explained to it in more detail, this invention is not limited by these at all.

[0028] Example 11 of reference -(2-O-tert-butyldimethylsilyl-3-C-trimethylsilyl ethynyl-beta-D-RIBO-PENTO furanosyl)- Manufacture (1) 1 of 5-methyluracil -(2 5-O-G tert-butyldimethylsilyl-beta-D-RIBO-PENTO furanosyl)- 5-methyluracil tert-buthyldimethyl silyl chloride (it abbreviates to "TBS chloride" below) (6.60g, 44.0mmol), and silver nitrate (7.50g, 44.0mmol) It dissolved in the tetrahydrofuran (200mL) and stirred for 5 minutes. Thymidine (5.16g, 20.0mmol) and a pyridine (8.00mL, 99.0mmol) were added there, and it stirred at the room temperature under the argon ambient atmosphere for 17 hours. TBS chloride (660mg, 4.40mmol), the silver nitrate (1.50g, 8.80mmol), and the pyridine (1.60mL, mmol) were added to the reaction solution, and it stirred for further 6 hours. Cerite filtration of the reaction mixed liquor was carried out, ethanol (10mL) was added to filtrate, and the bottom solvent of reduced pressure was distilled off. Residue was distributed to ethyl acetate (100mL) and the thing which added 1-N hydrochloric-acid water solution (15mL) to water (100mL), water (100mL) and saturation brine (100mLx2) washed the organic layer, and it dried with anhydrous sodium sulfate. The bottom solvent of reduced pressure was distilled off for filtrate after filtration, the silica gel column chromatography (phi7.5x13cm, 25% ethyl acetate / hexane) refined residue

after ethanol azeotropy, and the mark compound (6.90g, 71%) was obtained as quality of non-variety entertainments.
[0029] FAB-MS(LR):m/z 487(MH+,100%).
FAB-MS(HR):Calcd for C22H43N2O6Si2:487.2657.Found:487.2650.1 H-NMR delta; 8.26 (brs, 1H, NH, D2O exchangeable) (CDCl3), 7.51 (s, 1H, H-6) 6.02 (d, 1H, H-1, J1', 2'=5.6Hz), 4.20 (dd, 1H, and H-2', J2', and 1 -- '=5.6Hz, J2', and 3'=5.3Hz) -- 4.12 (m, 1H, and H-4', J4', and 5 -- 'a=J4' and 5 -- ' -- b= 1.8Hz) -- 4.09 (m -- one -- H -- H - three -- ' -- J -- three -- ' -- two -- ' -- = -- 5.3 -- Hz -- J -- three -- ' -- OH -- = -- 3.5 -- Hz) -- 3.95 (dd, 1H, and H-5'a, J5'a, 4'=1.8Hz, J5'a, 5'b=11.5Hz), 3.81 (dd, 1H, and H-5'b, J5'b, 4'=1.8Hz, J5'b, 5'a=11.5Hz), 2.72 (d, 1H, 3' - OH, JOH, 3'=3.5Hz, D2O exchangeable), 1.93 (s, 3H, 5-Me) and 0. -- 95, 0.89 (each s, each 9H, t-Bu), 0.14, 0.13, and 0. -- 06 and 0.05 (each s, each 3H, Me)
Anal.Calcd for C22H42N2O6Si2:C,54.29;H,8.70;N,5.76.Found:C,54.32;H,8.66;N,5.74.
[0030] (2) 1 -(2 and 5-O-G tert - butyldimethylsilyl-3-oxo--beta-D-RIBO-PENTO furanosyl)- Molecular-sieves 4A (2.00g) heated for 80 seconds with the microwave oven was added to the 5-methyluracil methylene chloride (10mL), and chrome oxide (600mg, 6.0mmol) was quickly ice-cooled under ******** and an argon ambient atmosphere. Stirring this thing, the pyridine (490microL, 6.10mmol) was added, it stirred for 30 minutes, the acetic anhydride (570microL, 6.0mmol) was added, and it stirred for 10 more minutes. 1 dissolved in the methylene chloride (4.0mL) at this thing -(2 5-G O-tert-butyldimethylsilyl-beta-D-RIBO-PENTO furanosyl)- 5-methyluracil (970mg, 2.0mmol) was dropped over 5 minutes, and it stirred for 30 minutes with 0 degree C. After reaction mixed liquor was dropped at the ether (60mL), it stirred for 30 minutes and suction filtration was carried out by the funnel. The bottom solvent of reduced pressure was distilled off for filtrate, residue was distributed to ethyl acetate (20mL) and the thing which added 1-N hydrochloric-acid water solution (5mL) to water (20mL), a saturation sodium-hydrogencarbonate water solution (20mL), water (20mLx2), and saturation brine (20mL) washed the organic layer, and it dried with anhydrous sodium sulfate. After filtration, the bottom solvent of reduced pressure was distilled off for filtrate, and the mark compound (813mg, 84%) was obtained as a colorless compound.
[0031] FAB-MS(LR):m/z 485(MH+,72.9%).
FAB-MS(HR):Calcd for C22H41N2O6Si2:485.2500.Found:485.2531.
1 H-NMR delta; 8.20 (brs, 1H, NH, D2O exchangeable) (CDCl3), 7.51(s,1H,H-6),6.22(d,1H,H-1',J1',2'=8.3Hz),4.22 (brs,1H,H-4'),4.19(d,1H,H-2',J2',1'=8.3Hz),3.93(t,2H,H-5'ab),1.97(s,3H,5-Me)0.92,0.86(each s,each 9H,t-Bu),0.11,0.09,0.08,0.00(each s,each 3H,Me).
Anal.Calcd for C22H40N2O6Si2:C,54.51;H,8.32;N,5.78.Found:C,54.39;H,8.07;N,5.85.
[0032] (3) 1-(2-O-tert - butyldimethylsilyl-3-oxo--beta-D-RIBO-PENTO furanosyl)-5-methyluracil 1-(2 and 5-O-G tert - butyldimethylsilyl-3-oxo--beta-D-RIBO-PENTO furanosyl)-5-methyluracil (730mg, 1.50mmol) -- trifluoroacetic acid: -- the mixed liquor (4.5mL) of water =10:1 was added, and it stirred for 20 minutes at 0 degree C. A reaction solution is distributed to chloroform (25mL) and iced water (25mL), Water (20mL) washes an organic layer, and it adds until a water layer becomes neutrality about a saturation sodium-hydrogencarbonate water solution, without throwing away water. After it washes again and water (20mL) and saturation brine (20mL) wash further, it dries with anhydrous sodium sulfate. The bottom solvent of reduced pressure is distilled off for the filtrate after filtration, and it is a short silica gel column chromatography about residue. (phi3.6x9cm, 50% ethyl acetate / hexane) It refined and the mark compound (460mg, 82%) was obtained as quality of non-variety entertainments.
[0033] 1 H-NMR delta; 8.38 (br s, 1H, NH, D2O exchangeable) (CDCl3), 7.23(d,1H,H-6,J6,Me=1.0Hz),5.64(d,1H,H-1',J1',2'=7.7Hz), 4.76(d,1H,H-2',J2',1'=7.7Hz),4.25(dd,1H,H-4',J4',5'a=2.7Hz,J4',5'b=1.9Hz), 3.95(ddd,1H,H-5'a,J5'a,4'=2.7Hz,J5'a,OH=2.8Hz,J5'a,5'b=12.1Hz), 3.91(ddd,1H,H-5'b,J5'b,4'=1.9Hz,J5'b,OH=8.2Hz,J5'a,5'b=12.1Hz, 3.00 (dd, 1H, 5' - OH, JOH, 5'a=2.8Hz, JOH, 5'b=8.2Hz), 1.97 (3 d, H, 5- Me, JMe, 6= 1.0Hz), 0.86 (s, 9H, t-Bu), and 0. -- 12 and 0.03 (each s, each 3H, Me)
Anal.Calcd for C16H26N2O6Si:C,51.87;H,7.07;N,7.56.Found:C,51.61;H,7.15;N,7.45.
[0034] (4) 1 -(2-O-tert-butyldimethylsilyl-3-C-trimethylsilyl ethynyl-beta-D-RIBO-PENTO furanosyl)- 5-methyluracil 1 -(2-O-tert - butyldimethylsilyl-3-oxo--beta-D-RIBO-PENTO furanosyl)- 5-methyluracil (4.00g, 10.8mmol) was made to react under the same conditions as the example 2 of the after-mentioned reference. The reaction was completed in 2 hours. Ethyl acetate (300mL) and water (100mL) distributed reaction mixed liquor, a saturation sodium-hydrogencarbonate water solution (100mLx2), water (100mL), and saturation brine (100mL) washed the organic layer, and it dried with anhydrous sodium sulfate. The bottom solvent of reduced pressure was distilled off for filtrate after filtration, the silica gel column chromatography (phi7.5x14cm, 45% ethyl acetate / hexane) refined residue, and the mark compound (3.85g, 76%) was obtained as a light yellow solid-state.
[0035] FAB-MS(LR):m/z 469(MH+,87.5%).
FAB-MS(HR):Calcd for C21H37N2O6Si2:469.2188.Found:469.2218.
1 H-NMR delta; 8.17 (brs, 1H, NH, D2O exchangeable) (CDCl3), 7.50(d,1H,H-6,J6,Me=1.0Hz),5.81(d,1H,H-1',J1',2'=7.0Hz), 4.49(d,1H,H-2',J2',1'=7.0Hz),4.18(t,1H,H-4',J4',5'a=J4',5'b=2.8Hz), 4.02(ddd,1H,H-5'a,J5'a,4'=2.8Hz,J5'a,OH=6.2Hz,J5'a,5'b=12.5Hz), 3.89(ddd,1H,H-5'b,J5'b,4'=2.8Hz,J5'b,OH=6.2Hz,J5'a,5'b=12.5Hz),

3.30 (s, 1H and 3'-OH, D2O exchangeable), 2.49 (t, 1H, 5' - OH, JOH, 5 'a=JOH, 5' b= 6.2Hz D2O exchangeable), 1.95 (3 d, H, 5- Me, JMe, 6= 1.0Hz), 0.90 (s, 9H, t-Bu), 0.20 (s, 9H, TMS), and 0. -- 14 and 0.00 (each s, each 3H, Me)
Anal.Calcd for:C21H36N2O6Si2:C,53.82;H,7.74;N,5.98.Found:C,54.03;H,7.74;N,5.94.
[0036] Manufacture cerium chloride 7 hydrate (38.0g, 102mmol) of an example of reference 21-(2-O-tert-butyldimethylsilyl-3-C-trimethylsilyl ethynyl-beta-D-RIBO-PENTO furanosyl) uracil was decompressed with the vacuum pump, and it stirred at 150 degrees C for 7 hours. It returned to ordinary pressure, introducing argon gas into this thing, and the bottom tetrahydrofuran of ice-cooling (120mL) was added, and it returned to the room temperature, and stirred overnight. Apart from this thing, the tetrahydrofuran (70mL) was added to trimethylsilyl acetylene (14.5mL, 102mmol), it cooled at -20 degrees C under the argon ambient atmosphere, the hexane solution (1.68M, 61mL, 102mmol) of butyl lithium was dropped over 30 minutes, and it stirred at this temperature for 30 minutes. Cannulation was carried out to the suspension of previous cerium chloride, having applied [this] it to what was cooled at -78 degrees C for 20 minutes. The suspension of the obtained yellow is stirred for 60 minutes at this temperature, and it is 1. -(2-O-tert - butyldimethylsilyl-3-oxo--beta-D-RIBO-PENTO furanosyl)- The tetrahydrofuran solution (34.0mL) of a uracil (6.0g, 17.0mmol) was dropped over 15 minutes, and it stirred at -78 degrees C for 2 hours. The acetic acid (15.0mL) was added to reaction mixed liquor, after carrying out a temperature up to a room temperature, it distributed to ethyl acetate (500mL) and water (200mL), and water (200mLx2) and saturation brine (200mL) washed the organic layer, and it dried with anhydrous sodium sulfate. The solvent was distilled off under reduced pressure after filtration, after suspending residue in a hexane, it separated, and the mark compound (6.63g, 86.7%) was obtained as solid-state-like matter.
[0037] FAB-MS(LR):m/z 455(MH+,64.8%).
FAB-MS(HR):Calcd for C20H35N2O6Si2:455.2031.Found:455.2004.
1 H-NMR delta; 11.37 (brs, 1H, NH, D2O exchangeable) (DMSO-d6), 8.23(d,1H,H-6,J6,5=8.1Hz),5.88(d,1H,H-1',J1',2'=7.3Hz), 5.80(s,1H,3'-OH,D2Oexchangeable), 5.71(dd,1H,H-5,J5,6=8.1Hz),5.10(br-s,1H,5'-OH,D2O exchangeable), 4.34(d,1H,H-2',J2',1'=7.3Hz),3.94(t,1H,H-4'), 3.73(m,1H,H-5'a,J5a',5'b=11.8Hz), 3.66(m,1H,H-5'b,J5'b, 5'a=11.8Hz, 0.81 (s, 9H, t-Bu) and 0.14 (s, 9H, TMS), 0.88, -0.05 (each s, each 3H, Me)
Anal.Calcd for C20H34N2O6Si2.0.1H2 O:C, 52.63;H, 7.55;N, 6.14.Found:C, 52.39;H, 7.80;N, 6.09
[0038] It dissolved in the tetrahydrofuran (200mL) and the manufacture (1)9-(2 5-O-G tert-butyldimethylsilyl-beta-D-RIBO-PENTO furanosyl) adenine TBS chloride (8.10g, 53.7mmol) of an example of reference 39-(2-O-tert-butyldimethylsilyl-3-C-triisopropyl silyl ethynyl-beta-D-RIBO-PENTO furanosyl) adenine and a silver nitrate (9.20g, 54.2mmol) were stirred for 5 minutes. The adenosine (5.35g, 20.0mmol) and the pyridine (8.90mL, 110mmol) were added there, and it stirred at the room temperature under the argon ambient atmosphere for 17.5 hours. Reaction mixed liquor was filtered, ethanol (10mL) was added to filtrate, and the bottom solvent of reduced pressure was distilled off. Residue was distributed to ethyl acetate (250mL) and the thing which added water (200mL ** 1N hydrochloric-acid water-solution 10mL), a saturation sodium-hydrogencarbonate water solution (200mL), water (200mL), and saturation brine (200mL) washed the organic layer, and it dried with anhydrous sodium sulfate. The bottom solvent of reduced pressure was distilled off for filtrate after cotton plug filtration, residue was dissolved in a small amount of chloroform, the silica gel column chromatography (7.5x15+1.2cm, 50/25/25 - 60 / 20/20% ethyl acetate / hexane / chloroform) refined, and the mark compound (5.44g, 55%) was obtained as colorless crystal-like matter.
[0039] FAB-MS(LR):m/z 496 (MH+,100%).
FAB-MS(HR):Calcd for C22H42N5O4Si2:496.2773.Found:496.2795.
1H-NMR(CDCl3) delta; -- 8.35 (s, 1H, H-8) and 8.21 (s, 1H, H-2), 6.10(d,1H,H-1',J1',2'=5.0Hz),5.62(br s,2H,NH2,D2O exchangeable), 4.65(t,1H,H-2',J2',1'=J2',3'=5.0Hz), 4.28(dd,1H,H-3',J3',2'=5.0Hz,J3',OH=8.2Hz), 4.20 (dd,1H,H-4',J4',5'a=2.6Hz,J4',5'b=2.5Hz), 4.01(dd,1H,H-5'a,J5'a,4'=2.6Hz,J5'a,5'b=11.4Hz), 3.86(dd,1H,H-5'b, J5'b, 4'=2.5Hz, J5'b, 5'a=11.4Hz, 2.74 (d, 1H, 3' - OH, d, 1H, 3' - OH, JOH, 3'=8.2Hz, D2O exchangeable), 0. 96, 0.84 (each s, each 9H, t-Bu), 0.15, 0.14, -0.03, -0.14 (each s, each 3H, Me)
Anal.Calcd for C22H41N5O4Si2:C,53.18;H,8.29;N,14.28.Found:C,53.30;H,8.34;N,14.13.
[0040] (2) Molecular-sieves 4A (1.00g) heated for 80 seconds with the microwave oven was added to 9-(2 and 5-O-G tert - butyldimethylsilyl-3-oxo--beta-D-RIBO-PENTO furanosyl) adenine methylene chloride (5.00mL), and chrome oxide (300mg, 3.00mmol) was quickly ice-cooled under ******** and an argon ambient atmosphere. Stirring this thing, the pyridine (240mL, 3.00mmol) was added, it stirred for 30 minutes, the acetic anhydride (280mL, 3.00mmol) was added, and it stirred for 10 minutes. 9-(2 5-O-G tert-butyldimethylsilyl-beta-D-RIBO-PENTO furanosyl) adenine (500mg, 1.00mmol) which dissolved in the methylene chloride (5mL) was added to this thing, and it stirred for 30 minutes with 0 degree C. After reaction mixed liquor was dropped at ethyl acetate (100mL), it stirred for 30 minutes and suction filtration was carried out by the funnel. Abbreviation one half distilling off of the bottom solvent of reduced pressure was carried out for filtrate, and it is what added 1-N hydrochloric-acid water solution (2mL) to water (50mL), and washed, a saturation sodium-hydrogencarbonate water solution (50mLx2), water (50mL), and saturation brine (30mL) washed the organic layer, and it dried with anhydrous sodium sulfate. Distilled off the bottom solvent of

reduced pressure, filtrate was made to suspend in a hexane after filtration, the solid-state was separated, and the mark compound (463mg, 93%) was obtained as a colorless crystal-like compound.
[0041] FAB-MS(LR):m/z 494(MH+,60.8%).
FAB-MS(HR):Calcd for C22H40N5O4Si2:494.2616.Found:494.2639.
1H-NMR(CDCl3) delta; -- 8.37 (s, 1H, H-8) and 8.14 (s, 1H, H-2), 6.13(d,1H,H-1',J1',2'=8.2Hz),5.65 (brs,2H,NH2,D2O exchangeable), 4.94(d,1H,H-2',J2',1'=8.2Hz),4.30(br s,1H,H-4'), 3.99(dd,1H,H-5'a,J5'a,4'=2.4Hz,J5'a,5'b=11.3Hz), 3.95(dd,1H,H-5'b,J5'b,4'=2.3Hz,J5'b,5'a=11.3Hz), 0.92,0.73(each s,each 9H,t-Bu),0.11,0.0 [7], -0.01, -0.20 (each s, each 3H, Me)
Anal.Calcd for C22H39N5O4Si2:C,53.52;H,7.96;N,14.18. Found:C,53.40;H,7.88;N,14.18.
[0042] (3) The mixed liquor (1.50mL) of trifluoroacetic acid:water =10:1 was added to the 9-(2-O-tert - butyldimethylsilyl-3-oxo--beta-D-RIBO-PENTO furanosyl) adenine 9-(2 and 5-O-G tert - butyldimethylsilyl-3-oxo--beta-D-RIBO-PENTO furanosyl) adenine (250mg, 0.50mmol), and it stirred for 20 minutes at 0 degree C. A reaction solution is distributed to chloroform (25mL) and iced water (25mL), Water (20mL) washes an organic layer, and in addition, it washes again until a water layer becomes neutrality about a saturation sodium-hydrogencarbonate water solution, without throwing away water. Furthermore, after water (20mL) and saturation brine (20mL) wash, it dries with anhydrous sodium sulfate. Distilled off the bottom solvent of reduced pressure for the filtrate after filtration, after writing residue with a spatula for residue by chloroform/hexane, once distilled off the bottom solvent of reduced pressure, and the hexane was made to **** the obtained solid-state, the solid-state was separated, and the mark compound (146mg, 76%) was obtained.
[0043] FAB-MS(LR):m/z 380(MH+,6.7%).FAB-MS(HR):Calcd for C16H26N5O4Si:380.1752.Found:380.1779.
1 H-NMR delta; 8.51 (s, 1H, H-8) (DMSO-d6), 8.16(s,1H,H-2),7.43(br s,2H,NH2,D2O exchangeable), 6.16(d,1H,H-1',J1',2'=8.1Hz),5.54(br s,1H,5'-OH,D2O exchangeable), 5.07(d,1H,H-2',J2',1'=8.1Hz),4.42(t like dd,1H,H-4',J4',5'a=2.5Hz,J4',5'b=2.9Hz), 3.71(dd,1H,H-5'a,J5'a,4'=2.5Hz,J5'a,5'b=12.6Hz), 3.66 (dd, 1H, and H-5'b, J5'b, 4'=2.9Hz, J5'b, 5'a=12.6Hz), 0.67 (s, 9H, t-Bu), -0.14, -0.29 (each s, each 3H, Me)
Anal.Calcd for C16H25N5O4Si.15H2O:C,50.28;H,6.67;N,18.32.Found:C,50.56;H,6.76;N,18.04.
[0044] (4) 9-(2-O-tert-butyldimethylsilyl-3-C-triisopropyl silyl ethynyl-beta-D-RIBO-PENTO furanosyl) adenine cerium chloride 7 hydrate (23.0g, 61.7mmol) was decompressed with the vacuum pump, and it stirred at 160 degrees C for 4.5 hours. It returned to ordinary pressure, introducing argon gas into this thing, and the bottom tetrahydrofuran of ice-cooling (75.0mL) was added, and it returned to the room temperature, and stirred overnight. Apart from this thing, the tetrahydrofuran (20mL) of triisopropyl silyl acetylene (13.8mL, 61.6mmol) was added, it cooled at 0 degree C under the argon ambient atmosphere, the hexane solution (1.68M, 36.7mL, 61.7mmol) of butyl lithium was dropped over 10 minutes, and it stirred at this temperature for 30 minutes. This thing was cooled at -15 degrees C, and cannulation was carried out to it, having applied [of previous cerium chloride] it to what was cooled at -78 degrees C for 20 minutes. The suspension of the obtained yellow was stirred for 90 minutes at this temperature, and the tetrahydrofuran solution (150mL) of 9-(2-O-tert - butyldimethylsilyl-3-oxo--beta-D-RIBO-PENTO furanosyl) adenine (3.90g, 10.3mmol) was dropped over 10 minutes, and it stirred for 60 minutes at -78 degrees C. The acetic acid (8.80mL) was added to reaction mixed liquor, after carrying out a temperature up to a room temperature, it distributed to ethyl acetate (300mL) and water (100mL), and a saturation sodium-hydrogencarbonate water solution (100mLx2), water (100mL), and saturation brine (100mL) washed the organic layer, and it dried with anhydrous sodium sulfate. The solvent after filtration was distilled off under reduced pressure, the silica gel column chromatography (phi7.5x15cm, 50 - 75% ethyl acetate / hexane) refined residue, and the mark compound (3.93g, 68.1%) was obtained as colorless solid-state-like matter.
[0045] FAB-MS(LR):m/z 562(MH+,58.8%).
FAB-MS(HR):Calcd for C27H48N5O4Si2:562.3242.Found:562.3239.
1H-NMR(CDCl3) delta; -- 8.39 (s, 1H, H-8) and 7.79 (s, 1H, H-2), 6.31(dd,1H,5'-OH,JOH,5'a=11.3Hz,JOH,5'b=2.3Hz,D2O exchangeable), 5.75(d,1H,H-1',J1',2'=7.6 Hz), 5.67(br s,2H,NH2,D2O exchangeable), 5.21(d,1H,H-2',J2',1'=7.6Hz),4.31(br.s,1H,H-4'), 4.02(dd,1H,H-5'a,J5'a,OH=11.3Hz,J5a',5'b=13.0Hz), 3.96(dd,1H,H-5'b,J5'b, OH'=2.3Hz, J5'b, 5'a=13.0Hz, 3.21 (s, 1H and 3'-OH, D2O exchangeable), 1.12 (s, 21H, -Sii-Pr3), 0.81 (s, 9H, t-Bu), 0.03, -0.49 (each s, each 3H, Me)
Anal.Calcd for C27H47N5O4Si2:C,57.72;H,8.43;N,12.46.Found:C,57.63;H,8.45;N,12.46.
[0046] Example 11- (2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) manufacture (1)1- (3 --) of a uracil (compound 1) 5-G O-benzoyl-2-O-tert-butyldimethylsilyl-3-C-trimethylsilyl ethynyl-beta-D-RIBO-PENTO furanosyl uracil 1 - () [2] - O-tert-butyldimethylsilyl-3-C-trimethylsilyl ethynyl-beta-D-RIBO-PENTO furanosyl uracil (2.65g, 5.80mmol) It dissolved in the acetonitrile (60mL), a benzoic anhydride (3.90g, 17.2mmol) and DMAP (2.10g, 17.2mmol) were added, and it stirred at the room temperature under the argon ambient atmosphere for 2 hours. After adding 7-8 grains of ice to reaction mixed liquor, it checked that the spot of the TLC top benzoic anhydride origin had disappeared, and the bottom solvent of reduced pressure was distilled off. After it distributed residue to what added 1-N

hydrochloric-acid water solution (5mL) to ethyl acetate (50mL) and water (50mL) and a saturation sodium-hydrogencarbonate water solution (50mx2), water (50mL), and saturation brine (50mL) washed the organic layer, it dried with anhydrous sodium sulfate. Bottom solvent distilling off of reduced pressure of the filtrate was carried out after filtration. The silica gel column chromatography (the 1st time: phi3.6x20cm, 33% ethyl acetate / hexane, the 2nd time : 3.5x18cm, 50% ether / hexane) refined residue, and the mark compound (3.26g, 84%) was obtained as quality of non-variety entertainments.

[0047] FAB-MS(LR):m/z 663(MH+,18.8%).

FAB-MS(HR):Calcd for C34H43N2O8Si2:663.2555.Found:663.2553.

1 H-NMR (CDCl3) delta; 8.13 to 8.05, 7.62 to 7.41, [11H, Bz and NH, D2O exchangeable (NH)], 7.78 (d, 1H, H-6, J6, 5= 8.2Hz), 6.21 (H[d, 1H, and]-1', J1', 2'=4.2Hz) 5.71 (d, 1H, and H-2', J2', 1'=4.2Hz), 5.67 (dd, 1H, H-5, J5, 6= 8.2Hz) 4.75 (dd, 1H, and H-5'a, J5'a, 4'=6.2Hz, J5'a, 5'b=12.3Hz), 4.68 (dd, 1H, and H-5'b, J5'b, 4'=2.5Hz, J5'b, 5'a=12.3Hz), 4.41 (dd, 1H, and H-4', J4', and 5 -- 'a= 6.2Hz, J4', 5' -- b= 2.5Hz), 0.78 (s, 9H, t-Bu), and 0. -- 26 and 0.15 (each s, each 3H, Me) 0.14 (s, 9H, TMS)

Anal.Calcd for C34H42N2O8Si2.0.55H2 O:C, 60.70;H, 6.46;N, 4.16.Found:C, 60.94;H, 6.24;N, 3.86

[0048] (2) 1-(3, 5-G O-benzoyl - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) uracil 1-(3 5-G O-benzoyl-2-O-tert-butyldimethylsilyl-3-C-trimethylsilyl ethynyl-beta-D-RIBO-PENTO furanosyl) uracil (1.00g, 1.50mmol) It dissolved in the tetrahydrofuran (15mL), the acetic acid (220microL, 3.75mmol), and the tetrabutylammoniumfluolide (TBAF) / tetrahydrofuran solution (1 N, 3.6mL, 3.6mmol) were added, and it stirred for 5 minutes at the room temperature. The bottom solvent of reduced pressure was distilled off for the reaction solution, the silica gel column chromatography (phi3.1x21.5+1.5cm, 50 - 67% ethyl acetate / hexane) refined residue, and the mark compound (690mg, 96%) was obtained as quality of non-variety entertainments.

[0049] FAB-MS(LR):m/z 477(MH+,20.8%).

FAB-MS(HR):Calcd for C25H21N2O8:477.1297.Found:477.13131 H-NMR delta; 8.54 (br, 1H, NH, D2O exchangeable) (CDCl3), 8.09 to 8.04, and 7.62- 7.41 (10H, Bz) and 7.65 (d, 1H, H-6, J6, 5= 8.2Hz) -- 6.34 (H[d, 1H, and]-1', J1', 2'=4.5Hz) 5.67 (d, 1H, H-5, J5, 6= 8.2Hz), 5.63 (H[d, 1H, and]-2', J2', 1'=4.5Hz) 4.79 (dd, 1H, and H-5'a, J5'a, 4'=5.7Hz, J5'a, 5'b=12.3Hz), 4.73 (dd, 1H, and H-5'b, J5'b, 4'=3.1Hz, J5'b, 5'a=12.3Hz), 4.49 (dd, 1H, and H-4', J4', and 5 -- 'a= 5.7Hz, J4', 5' -- b= 3.1Hz), 3.35 (br s, 1H, 2'-OH, D2O exchangeable), and 2.78 (s, 1H, 3'-C-C**CH)

Anal.Calcd for C25H20N2O8.0.5H2 O:C, 61.86;H, 4.36;N, 5.77.Found:C, 61.91;H, 4.33;N, 5.47

[0050] (3) 1-(3, 5-G O-benzoyl-2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) uracil 1-(3, 5-G O-benzoyl - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) uracil (650mg, 1.36mmol) It dissolved in the methylene chloride (14mL), 1 and 1'-thio carbonyldiimidazole (540mg, 2.73mmol) was added, and it stirred at the bottom room temperature of an argon ambient atmosphere for 17 hours. The reaction solution was distributed to chloroform (10mL) and water (30mL), the organic layer was dried with anhydrous sodium sulfate after washing with water (30mLx2) and saturation brine (30mL), and the bottom solvent of after [filtration] reduced pressure was distilled off. Benzene (100mL) and a tetrahydrofuran (20mL) were added to residue, it dissolved in it, azobisuisobutironitoriru (67.0mg, 0.41mmol) and tributyltin hydride (1.10mL, 4.09mmol) were added, and heating stirring was carried out for 5 minutes at 80 degrees C. The reaction solution was cooled to the room temperature, anhydrous potassium-fluoride 3 spoon and water (3mL) were added, and it stirred violently for 4 hours. Furthermore anhydrous sodium sulfate was added, cerite filtration was carried out, and the solvent of filtrate was distilled off under reduced pressure. Residue was distributed to ethyl acetate (30mL) and 1M potassium-fluoride water solution (30mL), after filtering the organic layer, water (30mLx2) and saturation brine (30mL) washed again, and it dried with anhydrous sodium sulfate. The bottom solvent of reduced pressure was distilled off for filtrate after filtration, the silica gel column chromatography (phi3.5x10cm, 50% ethyl acetate / hexane) refined residue, and it distributed to the acetonitrile (80mL) and the hexane (50mL) further, and distributed to the acetonitrile (80mL) and the hexane (50mL), and the acetonitrile layer was washed by the hexane (50mLx2). The bottom solvent of reduced pressure was distilled off, the silica gel column chromatography (phi3.5x10cm, 50% ethyl acetate / hexane) refined residue, and the mark compound (368mg, 59%) was obtained as quality of non-variety entertainments.

[0051] EI-MS(LR):m/z 460 (M+,0.02%)

EI-MS(HR):Calcd for C25H20N2O7:460.1269.Found:460.12591 H-NMR delta; 8.62 (br s, 1H, NH, D2O exchangeable) (CDCl3), 8.09- 7.44 (11H, Bz, H-6) and 6.37 (dd, 1H, and H-1', J1', and 2 -- 'a= 6.2Hz, J1', 2' -- b= 7.4Hz) -- 5.67 (d, 1H, H-5, J5, 6= 8.2Hz) 4.88 (d, 2H, H-5'ab, J5'ab, 4'=4.6Hz), 4.78 (t, 1H, and H-4', J4', 5'ab=4.6Hz), 3.20 (dd, 1H, and H-2'a, J2'a, 1'=6.2Hz, J2'a, 2'b=14.5Hz), 2.85 (s, 1H, -C-C**CH), 2.79 (dd, 1H, and H-2'b, J2'b, 1'=7.4Hz, J2'b, 2'a=14.5Hz)

Anal.Calcd for C25H20N2O7.

5H2O:C,63.96;H,4.51;N,5.96.Found:C,64.22;H,4.52;N,5.75.

[0052] (4) The 1-(2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) uracil 1-(3, 5-G O-benzoyl-2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) uracil (50.0mg, 0.11mmol) was dissolved in the methanol (2mL), 5-N

sodium methylate / methanol solution (26microL, 0.13mmol) was added, and it stirred at the room temperature under the argon ambient atmosphere for 2.5 hours. 1-N hydrochloric-acid water solution was added to the reaction solution, and it neutralized, after distilling off a solvent under reduced pressure, melted to a small amount of methanol, it was made to stick to silica gel, the bottom solvent of reduced pressure was distilled off again, the silica gel column chromatography (phi1.1x11+1cm, 10% methanol / chloroform) refined residue, and the compound 1 (mg [26.0], 95%) was obtained as colorless crystal-like matter. In addition, the sample for analysis was recrystallized and obtained from ethanol.

[0053] EI-MS(LR):m/z 252(M+,1.10%)

EI-MS(HR):Calcd for C11H12N2O5:252.0745.Found:252.07521 H-NMR delta; 7.99 (d, 1H, H-6, J6, 5= 8.2Hz) (D2O), 6.28 (dd, 1H, and H-1', J1', and 2 -- 'a= 6.2Hz, J1', 2' -- b= 7.4Hz) -- 5.91 (d, 1H, H-5, J5, 6= 8.2Hz) 4.11 (m, 1H, and H-4'), 3.93 (m, 2H, H-5'ab) 3.18 (s, 1H, -C-C**CH), 2.74 (H[dd, 1H, and]-2'a, J2'a, 1'=6.2Hz, J2'a, 2'b=13.9Hz) 2.59 (dd, 1H, and H-2'b, J2'b, 1'=7.4Hz, J2'b, 2'a=13.9Hz)

63.34 (CH2) 13 C-NMR (MeOH) (C) delta:166.18, 152.2 (C), 142.20 (C), 102.60 (CH), 89.99 (CH), 85.74 (CH), 83.25 (CH), 76.78 (C), 73.94 (C), 47.49 (CH2)

Anal.Calcd for C11H12N2O5:C,52.38;H,4.80;N,11.10.Found:C,52.12;H,4.86;N,11.00.

[0054] Example 21- Manufacture (1)1-(3, 5-G O-benzoyl-2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) cytosine 1- of a cytosine (compound 2) (2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) (3, 5-G O-benzoyl-2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) Uracil (150mg, 0.33mmol) It dissolved in the acetonitrile (3mL) and triisopropyl benzenesulphonyl chloride (TPS chloride) (200mg, 0.66mmol), triethylamine (92microL, 0.66mmol), and DMAP (80mg, 0.65mmol) were added, it stirred at the bottom room temperature of an argon ambient atmosphere for 1 hour, dark aqueous ammonia (3.0mL) was added further, and it stirred at the room temperature for 20 minutes. The reaction solution was distributed to ethyl acetate (30mL) and water (10mL), 0.1-N hydrochloric-acid water solution (10mL), 0.5-N hydrochloric-acid water solution (10mL), water (10mLx4), and saturation brine (10mL) washed the organic layer, and it dried with anhydrous sodium sulfate. Filtrate was condensed under reduced pressure after filtration, residue was dissolved in a small amount of methanol, after making it stick to a silica gel column chromatography, reduced pressure distilling off of the solvent was carried out again, the silica gel column chromatography (phi1.6x12.5+2.0cm, 6% methanol / chloroform) refined, and the mark compound (136mg, 91%) was obtained as colorless solid-state-like matter.

[0055] EI-MS(LR):m/z 459 (M+,0.04%)

EI-MS(HR):Calcd for C25H21N3O6:459.1429.Found:459.1412.

1 H-NMR (CDCl3) delta; 8.10 to 8.00, 7.62-7.42 (m, 10H, Bz), 7.76 (d, 1H, H-6, J6, 5= 7.5Hz) and 6.37 (dd, 1H, and H-1', J1', and 2 -- 'a= 5.9Hz, J1', 2' -- b= 7.4Hz) -- 6.30-5.00 (br s, 2H, NH2, D2O exchangeable), 5.63 (d, 1H, H-5, J5, 6= 7.5Hz), 4.89-4.83 (m, 3H, H-5'ab, H-4'), 3.38 (dd, 1H, and H-2'a, J2'a, 1'=5.9Hz, J2'a, 2'b=14.5Hz), 2.78 (s, 1H, -C-C**CH), 2.69 (dd, 1H, and H-2'b, J2'b, 1'=7.4Hz, J2'b, 2'a=14.5Hz)

Anal.Calcd for C25H21N3O6.65H2O:C,63.73;H,4.77;N,8.92.Found:C,63.94;H,4.66;N,8.62.

[0056] (2) The 1-(2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) cytosine 1-(3, 5-G O-benzoyl-2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) cytosine (200mg, 0.44mmol) was dissolved in the methanol (8.8mL), 5-N sodium methylate / methanol solution (100microL, 1.20mmol) was added, and it stirred at the bottom room temperature of an argon ambient atmosphere for 1 hour. 1-N hydrochloric-acid water solution was added to the reaction solution, it neutralized, and the bottom solvent of reduced pressure was distilled off. Residue was dissolved in a small amount of methanol, after making it stick to a silica gel column chromatography, reduced pressure distilling off of the solvent was carried out again, the silica gel column chromatography (phi1.0x10+1cm, 20% methanol / chloroform) refined, and it distributed to water (10mL) and chloroform (10mL) further, and after chloroform (10mLx5) washed the water layer, the bottom solvent of reduced pressure was distilled off. The compound 2 (mg [109], quant) was obtained as colorless crystal-like matter. In addition, the sample for analysis was made into the hydrochloride, and was recrystallized and obtained from ethanol. mp: 105 degree C [0057] EI-MS(LR):m/z 251(M+,2.90%).

EI-MS(HR):Calcd for C11H13N3O4:251.0905.Found:251.0932.

1 H-NMR delta; 8.17 (d, 1H, H-6, J6, 5= 7.9Hz) (D2O), 6.22 (dd, 1H, and H-1', J1', and 2 -- 'a= 6.3Hz, J1', 2' -- b= 6.7Hz) -- 6.21 (d, 1H, H-5, J5, 6= 7.9Hz) and 4.17 (dd, 1H, and H-4', J4', and 5 -- 'a= 3.6Hz, J4', 5' -- b= 6.0Hz) -- 3.98 (dd, 1H, and H-5'a, J5'a, 4'=3.6Hz, J5'a, 5'b=12.5Hz), 3.93 (dd, 1H, and H-5'b, J5'b, 4'=6.0Hz, J5'b, 5'a=12.5Hz), 3.15 (s, 1H, -C-C**CH), 2.80 (dd, 1H, and H-2'a, J2'a, 1'=6.3Hz, J2'a, 2'b=14.0Hz), 2.57 (dd, 1H, and H-2'b, J2'b, 1'=6.7Hz, J2'b, 2'a=14.0Hz)

13C-NMR(MeOH-d4)

63.07 (CH2) delta:161.51 (C), 152.2 (C), 148.94 (C), 146.38 (CH), 94.53 (CH), 90.76 (CH), 83.25 (CH), 87.38 (CH), 82.89 (CH), 77.05 (C), 73.98 (C), 47.90 (CH2)

Anal.Calcd for C11H14ClN3O4.45H2O:C,44.66;H,5.08;N,14.21.Found:C,44.89;H,4.86;N,13.92.

[0058] Example 31- manufacture (1)1- (2-O-tert-butyldimethylsilyl -3 --) of (2-deoxy-3-C-ethynyl-beta-D-RIBO-

PENTO furanosyl)-5-methyluracil (compound 3) 5-G O-benzoyl-3-C-trimethylsilyl ethynyl-beta-D-RIBO-PENTO furanosyl-5-methyluracil 1 - () [2-O-tert-BUCHI] RUJIME chill silyl-3-C-trimethylsilyl ethynyl-beta-D-RIBO-PENTO furanosyl-5-methyluracil (470mg, 1.00mmol) It was made to react like an example 1 (1). The reaction was completed in 2 hours. Two grains of ice was added to the reaction solution, spot disappearance of the benzoic-acid origin was checked on TLC, the bottom solvent of reduced pressure was distilled off, residue was distributed to ethyl acetate (20mL) and the thing which added 1-N hydrochloric-acid water solution (5mL) to water (20mL), a saturation sodium-hydrogencarbonate water solution (20mLx2), water (20mL), and saturation brine (20mL) washed the organic layer, and it dried with anhydrous sodium sulfate. The bottom solvent of reduced pressure was distilled off for filtrate after filtration, the silica gel column chromatography (phi2.7x18cm, 29% ethyl acetate / hexane) refined residue, and the mark compound (618mg, 91%) was obtained as quality of non-variety entertainments.

[0059] FAB-MS(LR):m/z 677(MH+,43.8%).

FAB-MS(HR):Calcd for C35H45N2O8Si2:677.2711.Found:677.2755.

1 H-NMR(CDCl3) delta;8.16-7.44[12H, Bz and NH, H-6, D2O exchangeable (-- NH --) --] -- six . -- 33 -- (-- d -- one -- H -- H - one -- ' -- J -- one -- ' -- two -- ' -- = -- 5.8 -- Hz --) -- 5.82 (d, 1H, and H-2', J2', 1'=5.8Hz), 4.73 (dd, 1H, and H-5'a, J5'a, 4'=5.0Hz, J5'a, 5'b=12.4Hz), 4.67 (dd, 1H, and H-5'b, J5'b, 4'=2.7Hz, J5'a, 5'b=12.4Hz), 4.40 (dd, 1H, and H-4', J4', and 5 -- 'a= 5.0Hz, J4', and 5'b=5-Me), 0.87 (s, 9H, t-Bu), 0.25, and 0.15 (each s, each 3H, Me) and 0.10 (s, 9H, TMS)

Anal.Calcd for:C35H44N2O8Si2:C,62.10;H,6.55;N,4.14.Found:C,62.15;H,6.58;N,4.35.

[0060] (2) 1 -(3, 5-G O-benzoyl - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl)- 5-methyluracil 1 -(2-O-tert-butyldimethylsilyl -3, 5-G O-benzoyl-3-C-trimethylsilyl ethynyl-beta-D-RIBO-PENTO furanosyl)- 5-methyluracil (570mg, 0.84mmol) It was made to react on the same conditions as an example 1 (2). The reaction was completed in 6 minutes. The bottom solvent of reduced pressure was distilled off for the reaction solution, dissolved residue in a small amount of methanol, it was made to stick to silica gel, the bottom solvent of reduced pressure was distilled off again, the silica gel column chromatography (phi2.7x19+1.5cm, 50% ethyl acetate / hexane) refined, and the mark compound (399mg, 97%) was obtained as quality of non-variety entertainments.

[0061] FAB-MS(LR):m/z 491(MH+,2.1%).

FAB-MS(HR):Calcd for C26H23N2O8:491.1453.Found:491.1428.

1 H-NMR delta; 8.22 (br s, 1H, NH, D2O exchangeable) (CDCl3), 8.13- 7.44 (10H, Bz) and 7.42 (d, 1H, H-6, J6, Me=1.0Hz) -- 6.43 (H[d, 1H, and]-1', J1', 2'=5.7Hz) 5.72 (d, 1H, and H-2', J2', 1'=5.7Hz), 4.76 (t, 2H, H-5'ab, J5'ab, 4'=3.6Hz), 4.50 (t, 1H, and H-4', J4', 5'ab=3.6Hz), 3.20 (br s, 1H, 2'-OH, D2O exchangeable), 2.77 (s, 1H, 3'-C-C**CH), 1.66 (3 d, H, 5- Me, JMe, 6= 1.0Hz)

Anal.Calcd for:C26H22N2O8.2H2O:C,63.21;H,4.60;N,63.17;H,4.52;N,5.52.

[0062] (3) 1 -(2-deoxy - 3, 5-G O-benzoyl - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl)- 5-methyluracil 1 -(3, 5-G O-benzoyl - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl)- 5-methyluracil (826mg, 1.68mmol) was made to react under the same conditions as an example 1 (3). Thiocarbonyl imidazoyl-ization was completed in 31 hours and radical reduction was completed in 7 minutes. In addition, in radical reduction, the solvent used only benzene. 1-N potassium-fluoride water solution (50mx3), water (50mL), and saturation brine (50mL) washed the reaction solution, and it dried with anhydrous sodium sulfate. The bottom solvent of reduced pressure was distilled off for filtrate after filtration, residue was distributed by the acetonitrile (100mL) and the hexane (50mL), the acetonitrile layer was washed by the hexane (50mLx4), and the bottom solvent of reduced pressure was distilled off. The silica gel column chromatography (phi3.5x13cm, 45% ethyl acetate / hexane) refined residue, it distributed by the acetonitrile (50mL) and the hexane (50mL) again, the acetonitrile layer was washed by the hexane (50mLx3), and the mark compound (472mg, 59%) was obtained as quality of non-variety entertainments.

[0063] FAB-MS(LR):m/z 475(MH+,3.30%).

FAB-MS(HR):Calcd for C26H23N2O7:475.1504.Found:475.1475.

1 H-NMR delta; 8.22 (br s, 1H, NH, D2O exchangeable) (CDCl3), 8.16- 7.45 (10H, Bz) and 7.42 (s, 1H, H-6) -- 6.42 (dd, 1H, and H-1', J1', and 2 -- 'a= 5.9Hz, J1', 2' -- b= 8.1Hz) -- 4.90 (dd, 1H, and H-5'a, J5'a, 4'=3.6Hz, J5'a, 5'b=12.3Hz), 4.86 (dd, 1H, and H-5'b, J5'b, 4'=4.8Hz, J5'b, 5'a=12.3Hz), 4.79 (dd, 1H, and H-4', J4', and 5 -- 'a= 3.6Hz, J4', 5' -- b= 4.8Hz) -- 3.18 (dd, 1H, and H-2'a, J2'a, 1'=5.9Hz, J2'a, 2'b=14.4Hz), 2.86 (s, 1H, -C-C**CH), 2.74 (dd, 1H, and H-2'b, J2'b, 1'=8.1Hz, J2'b, 2'a=14.4Hz), 1.69 (s, 3H, 5-Me)

Anal.Calcd for:C26H23N2O7.8H2O:C,63.88;H,4.89;N,5.73.Found:C,63.95;H,4.76;N,5.74.

[0064] (4) 1 -(2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl)- 5-methyluracil 1 -(2-deoxy - 3, 5-G O-benzoyl - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl)- 5-methyluracil (400mg, 0.84mmol) was made to react under the same conditions as an example 1 (4). The reaction was completed in 6 hours. 1-N hydrochloric-acid water solution was added to the reaction solution, it neutralized, and the bottom solvent of reduced pressure was distilled off. Residue is dissolved in a small amount of methanol, after making it stick to silica gel, a silica gel column chromatography (phi1.7x14+2.5cm, 12% methanol / chloroform) refines the residue which distilled off the bottom solvent of reduced

pressure again, water (20mL) and chloroform (30mL) distribute further, chloroform (30mLx2) washes a water layer, and the bottom solvent of reduced pressure is distilled off. The compound 3 (mg [197], 88%) was obtained as quality of non-variety entertainments.
[0065] EI-MS(LR):m/z 266(M+,8.60%).
EI-MS(HR):Calcd for C12H14N2O5:266.0901.Found:266.0877.
1 H-NMR delta; 11.39 (br s, 1H, NH, D2O exchangeable) (DMSO-d6), 7.97(d,1H,H-6,JMe,6=1.1Hz),6.27(dd,1H,H-1',J1',2'a=5.8Hz,J1',2'b=8.7Hz), 6.25(s,1H,3'-OH,D2O exchangeable), 5.13(dd,1H,5'-OH,JOH,5'a=4.4Hz,JOH,5'b=4.7Hz,D2O exchangeable), 3.95(dd,1H,H-4',J4',5'a=3.1Hz,J4',5'b=4.7Hz), 3.81 (ddd,1H,H-5'a,J5'a,4'=3.1Hz,J5'a, OH=4.4Hz, J5'a, 5'b=11.8Hz, 3.77 (dt, 1H, and H-5'b, J5'b, 4'=J5'b, OH=4.7Hz, J5'b, 5'a=11.8Hz), 3.71 (s, 1H, -C-C**CH) 2.45 (dd, 1H, and H-2'a, J2'a, 1'=5.8Hz, J2'a, 2'b=12.9Hz), 2.39 (H[dd, 1H, and]-2'b, J2'b, 1'=8.7Hz, J2'b, 2'a=12.9Hz) 1.87 (3 d, H, 5- Me, JMe, 6= 1.1Hz)
Anal.Calcd for:C12H14N2O5:C,54.13;H,5.30;N,10.52.Found:C,54.00;H,5.46;N,10.22.
[0066] The manufacture (1)9-(3, 5-G O-benzoyl - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) adenine of an example 49-(2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) adenine (compound 4)
9-(2-O-tert-butyldimethylsilyl-3-C-triisopropyl silyl ethynyl-beta-D-RIBO-PENTO furanosyl) adenine (1.12g, 2.00mmol) was dissolved in the acetonitrile (20mL), DMAP (0.54g, 4.40mmol) and a benzoic anhydride (1.00g, 4.40mmol) were added, and it stirred for 60 minutes at 50 degrees C under the argon ambient atmosphere. Ice is added to a reaction solution, it stirs for 60 minutes, a reaction-under reduced pressure solution is condensed in an abbreviation moiety, and it is ethyl acetate (40mL), 0.1-N hydrochloric-acid water solution (40mL) distributed, a saturation sodium-hydrogencarbonate water solution (40mL), water (40mLx2), and saturation brine (40mL) washed the organic layer, after drying with anhydrous sodium sulfate, filtration removed this, the bottom solvent of reduced pressure was distilled off, and it dried at 40 degrees C under reduced pressure overnight. This compound was dissolved in the tetrahydrofuran (20mL), it cooled at 0 degree C, and the acetic acid (0.30mL, 5.00mmol), and the TBAF / tetrahydrofuran solution (1 N, 4.80mL, 4.80mmol) were added, and after stirring for 7 minutes, it stirred for 20 minutes at the room temperature. The bottom solvent of reduced pressure was distilled off for the reaction solution, the silica gel column chromatography (3.0x14+2cm, 3% methanol / chloroform) refined residue, and the mark compound (919mg, 92.3%) was obtained as colorless solid-state-like matter.
[0067] 1H-NMR(DMSO-d6) delta;8. -- 42 and 8.16 (each s, each 1H, H-2&H-8), 8.15- 7.62 (m, 10H, Bz) and 7.41 (br s, 2H, NH2, D2O exchangeable) -- 7.16 (s, 1H and 2'-OH, D2O exchangeable), 6.53 (H[d, 1H, and]-1', J1', 2'=6.6Hz) 6.44 (d, 1H, and H-2', J2', 1'=6.6Hz), 4.91 (dd, 1H, and H-5'a, J5'a, 4'=3.9Hz, J5'a, 5'b=12.1Hz), 4.86 (dd, 1H, and H-5'b, J5'b, 4'=6.1Hz, J5'b, 5'a=12.1Hz), 4.64 (dd, 1H, and H-4', J4', and 5 -- 'a= 3.9Hz, J4', 5' -- b= 6.1Hz), and 3.95 (s, 1H, 3'-C-C**CH)
[0068] (2) 6-N, N-dibenzoyl-9-(3 5-G O-benzoyl-3-C-ethynyl-2-O-thiocarbonyl imidazolyl-beta-D-RIBO-PENTO furanosyl) adenine 9-[3, and 5-G O-benzoyl-3-C-ethynyl-beta-D-RIBO-PENTO furanosyl adenine] (560mg, 1.00mmol) It suspended in the acetonitrile (10.0ml), and DMAP (0.61g, 4.90mmol) and a benzoyl chloride (580micromL) were added, and question stirring was carried out at bottom of argon ambient atmosphere 18:00. Two grains of ice is added to a reaction solution, question stirring is carried out for 60 minutes, a reaction-under reduced pressure solution is condensed twice, and it is ethyl acetate (30mL), It distributes to 0.1-N hydrochloric-acid water solution (20mL). An organic layer A saturation sodium-hydrogencarbonate water solution (30mL), After water (30mLx2) and saturation brine (40mL) washing and drying with anhydrous sodium sulfate, cotton plug filtration removes this. This thing is dissolved in a tetrahydrofuran (6.5mL). . which distilled off the bottom solvent of reduced pressure and was dried at 40 degrees C under reduced pressure overnight -- It cooled at 0 degree C and the acetic acid (93microL, 1.56mmol), and the TBAF / tetrahydrofuran solution (1.0 Ns, 1.40mL, 4.80mmol) were added, and after stirring for 7 minutes, it stirred for 20 minutes at the room temperature. Distilled off the bottom solvent of reduced pressure, the reaction solution was made to stick to silica gel after dissolving in a small amount of methanol, the bottom solvent of reduced pressure was distilled off again, this thing was refined by the silica gel column chromatography (phi3.0x14+2cm), and the 50% acetic-acid ETERU / hexane, this which was dried overnight was dissolved in the methylene chloride (5.0mL), 1 and 1-thio carbonyldiimidazole was added, and it stirred at the room temperature for 24 hours. 0.IN hydrochloric-acid water-solution (10mL) saturation carbonic acid hydrogen NATORIKUMU water-solution (10mL) water (10mL) and saturation brine (10mL) washed the reaction solution, and it dried with anhydrous sodium sulfate. Filtrate was condensed after filtration, the silica gel column chromatography (phi1.8x14.5 or 50% **** ethyl / hexane) refined residue, and the mark compound (269mg, 59.2%) was obtained as quality of non-variety entertainments.
[0069] FAB-MS(LR):m/z 818(MH+,45.8%).
FAB-MS(HR):Calcd for C44H32N7O8S:818.2032.1017. Found:818.2044.
1H-NMR(CDCl3) delta; -- 8.61 (s, 1H, H-8) and 8.58 (s, 1H, H-2), 8.14- 7.26 (22H, Bz, Im) and 6.91 (s, 1H, Im) -- 6.84 (H[d, 1H, and]-1', J1', 2'=3.8Hz) 6.59 (d, 1H, and H-2', J2', 1'=3.8Hz), 5.03 (dd, 1H, and H-5'a, J5'a, 4, '=3.6Hz,

J5'a, 5'b'=11.7Hz), 4.98 (dd, 1H, and H-4', J4', 5a, '=3.6Hz, J4', 5'b'=5.7Hz), 4.93 (dd, 1H, and H-5'b, J5'b, 4, '=5.7Hz, J5'b, 5'a=11.7Hz), 2.98 (1H, 3-C-C**CH)
Anal.Calcd for C44H31N7O8S and 0.2 AcOEt:C, 64.30;H, 3.94;N, 11.79. Found:C, 64.59;H, 4.22;N, 11.58
[0070] (3) 6-N and N-dibenzoyl - 9-(2-deoxy - 3, 5-G O-benzoyl - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) adenine 6-N-dibenzoyl-9-(3 5-G O-benzoyl-3-C-ethynyl-2-O-thiocarbonyl imidazolyl-beta-D-RIBO-PENTO furanosyl) adenine (220mg, 0.27mmol) Toluene azeotropy (X2) was carried out, it dissolved in benzene (27mL, thing which carried out bubbling of the argon gas for 30 minutes), and under the argon ambient atmosphere, the benzene solution (1.01mL) of tributyltin hydride (87microL, 0.32mmol) and azobisuisobutironitoriru (13mg, 0.08mmol) was added to there where heating reflux was carried out, and heating reflux was carried out for 20 minutes. The reaction solution was ice-cooled, it returned to the room temperature, and the bottom solvent of reduced pressure was distilled off. Residue was extracted by the acetonitrile (20mL) and it washed by the hexane (30mLx3). Carried out ****** concentration of this thing, dissolved residue in a small amount of chloroform, it was made to stick to silica gel, the bottom solvent of reduced pressure was distilled off again, the silica gel column chromatography (phi1.8x13+0.5cm, 40% ethyl acetate / hexane) refined this, and the mark compound (96mg, 51.6%) was obtained as quality of non-variety entertainments.
[0071] FAB-MS(LR):m/z 692(MH+,5.1%).
FAB-MS(HR):Calcd for C40H30N5O7:692.143.Found:692.2719.
1H-NMR(CDCl3) delta; -- 8.61 (s, 1H, H-8) and 8.40 (s, 1H, H-2), 8.04- 7.34 (20H, Bz) and 6.59 (dd, 1H, and H-1', J1', and 2 -- 'a= 7.4Hz, J1', 2' -- b= 6.4Hz) -- 4.94 (dd, 1H, and H-5'a, J5'a, 4'=3.0Hz, J5'a, 5b'=10.9Hz), 4.91 (dd, 1H, and H-4', J4', and 5 -- 'a= 3.0Hz, J4', 5' -- b= 5.6Hz) -- 4.87 (dd, 1H, and H-5'b, J5'b, 4, '=5.6Hz, J5'b, 5'a=10.9Hz), 3.51 (dd, 1H, and H-2'a, J2'a, 1, '=7.4Hz, J2'a, 2'b=14.3Hz), 3.33 (dd, 1H, and H-2'b, J2'b, 1, '=6.4Hz, J2'b, 2'a=14.3Hz), 2.85 (s, 1H, 3-C-C**CH)
Anal.Calcd for C40H29N5O7.0.7H2 O:C, 68.21;H, 4.35;N, 9.94.Found:C, 68.46;H, 4.46;N, 9.62
[0072] (4) 9-(2-deoxy - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) adenine 6-N and N-dibenzoyl-9-(2-deoxy - 3, 5-G O-benzoyl - 3-C-ethynyl-beta-D-RIBO-PENTO furanosyl) adenine (55mg, 0.08mmol) It dissolved in the methanol (1.6mL), 5-N sodium methylate / methanol solution (20microL, 0.1mmol) was added, and it stirred at the room temperature under the argon ambient atmosphere for 11.5 hours. 1-N hydrochloric-acid water solution was added to the reaction solution, it neutralized, the bottom solvent of reduced pressure was distilled off, the silica gel column chromatography (phi0.9x7.5+1cm, 12% methanol / chloroform) refined this, and the compound 4 (mg [25], quant) was obtained as colorless solid-state-like matter.
[0073] mp: 118-120 degree-CEI-MS(LR):m/z 275 (M+, 4.6%)
EI-MS(HR):Calcd for C12H13N5O3:275.1017.Found:275.1028.
1H-NMR(D2O) delta; -- 8.56 (s, 1H, H-8) and 8.43 (s, 1H, H-2), 6.54 (t like dd, 1H, and H-1', J1', and 2 -- 'a= 7.5Hz, J1', 2' -- b= 5.8Hz) -- 4.24 (H[br.s, 1H, and]-4') 4.01 (dd, 1H, and H-5'a, J5'a, 5'b'=12.5Hz), 3.95 (d, 1H, and H-5'b, J5b', 5'a, =12.5Hz), 3.18 (s, 1H, 3-C-C**CH), 3.09 (dd, 1H, and H-2'a, J2'a, 1, '=7.45Hz, J2'a, 2'b=13.2Hz), 2.89 (dd, 1H, and H-2'b, J2'b, 1, '=5.8Hz, J2'b, 2'a=13.2Hz)
13C-NMR(MeOH-d4)
delta:157.50 (C), 153.53 (C), 141.70 (C), 126.80 (C), 120.50 (C), 90.92 (CH), 86.23 (CH), 83.11 (CH), 76.57 (C), 74.37 (C), 63.77 (CH), 47.13 (CH)
[0074] Example 1 of a pharmacological test (killer cell operation)
Seeding of a Homo sapiens KB cell and the L1210 cell was carried out to 96 hole plate by 1x105 cells/well. RPMI after dissolving this invention compound in purified water It diluted to concentration various by 1640 MEDIUMU, and added and cultivated to each well. The number of cells was measured by the MTT method after the contact for 37 degrees C and three days by the CO2 incubator 5%. It expressed as drugs concentration (IC50) which decreases the number of cells of control of a killer cell operation of each compound 50%. A result is shown in Table 1.
[0075]
[Table 1]

化合物番号	IC_{50} (μg/ml)	
	KB細胞	L1210
化合物1	0.61	0.26

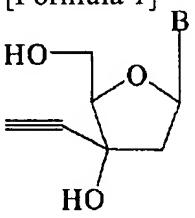
[0076] this invention compound showed very powerful killer cell activity so that clearly from this result.
[0077]
[Effect of the Invention] The new 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative of this invention has the antitumor activity which was excellent, for example, and is useful as an antitumor agent.

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] The 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative expressed with a general formula (1) and its ester from which it may be desorbed easily in the living body, or its salt permitted pharmacologically.
[Formula 1]



(1)

(B shows among a formula the nucleobase which may have a substituent.)
[Claim 2] The 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative according to claim 1 whose B is cytosine, uracil, thymine, adenine, guanine, 5-fluoro cytosine, 5-fluorouracil, 5-BUROMO cytosine, 5-bromouracil, 4-N-methylcytosine or 4-N, and N-dimethyl cytosine and its ester from which it may be desorbed easily in the living body, or its salt permitted pharmacologically.
[Claim 3] The 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative according to claim 2 whose B is a cytosine, a uracil, a thymine, and an adenine and its ester from which it may be desorbed easily in the living body, or its salt permitted pharmacologically.
[Claim 4] The ester from which it may be desorbed easily in the living body of a 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative given in any of claims 1-3 they are whose ester formation residue from which it may be desorbed easily in the living body is an acyl group, or its salt permitted pharmacologically.
[Claim 5] Physic which makes an active principle a 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative given in any of claims 1-4 they are, its ester from which it may be desorbed easily in the living body, or its salt permitted pharmacologically.
[Claim 6] The physic constituent characterized by containing a 2-deoxy-3-ethynyl-beta-D-ribofuranosyl derivative, its ester from which it may be desorbed easily in the living body or its salt permitted pharmacologically, and pharmacological support given in any of claims 1-4 they are.
[Claim 7] Physic according to claim 5 which is an antitumor agent.

[Translation done.]